TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

International Application No.	:	PCT/FR00/00495
International Filing Date	:	February 29, 2000
Priority Date Claimed	:	FR 99/02516 Filed on March 1, 1999
Title of Invention	:	ORALLY DISPERSIBLE TABLET WITH LOW FRIABILITY AND METHOD FOR PRODUCING SAME
Applicant(s) for DO/EO/US	:	Laurent DI COSTANZO Edouard André GENDROT Mathieu Ernest Jean-Baptiste DI COSTANZO Charles André CHAUVEAU

Box PCT
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Attention: EO/US

Sir:

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

3. A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

4. A copy of the International Application as filed (35 U.S.C 371(c)(2)) has been transmitted by the International Bureau. A copy of the cover sheet of international application as published on September 8, 2000, under International Publication No. WO 00/51568 is enclosed.

5. An English translation of International Application No. PCT/FR00/00495 is enclosed.

6. A FIRST preliminary amendment is enclosed.

7. An Abstract is attached to the preliminary amendment.

The Declaration and Assignment will follow at a later date.

8. The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(1)(1)-(5):

	For	Number Filed	Number Extra	Rate	Calculation
Claims Fee	Total Claims	12	0	x 18	$
	Independent Claims	1	0	x 80	
	Multiple Dependent Claims			x270	
Basic Fee	U.S. PTO was not International Preliminary Examination Authority. Search report on the international application was prepared by the European Patent Office				$ 860
	Total of above Calculations				$ 860
	Reduction by ½ for filing by small entity				
	Subtotal				$
	TOTAL NATIONAL FEE				**$ 860**

Please charge counsel's account no. 03-0075 in the amount of $860, or any additional amount which may be required, to cover the above fees. A duplicate copy of the calculation sheet is enclosed.

AUTHORIZATION TO CHARGE ADDITIONAL FEES

The Commissioner is hereby authorized to charge the following additional fees which may be required by this paper and during the entire pendency of this application to counsel's deposit account no. 03-0075:

1. 37 CFR 1.492(a)(1), (2), (3) and (4) (filing fees)

2. 37 CFR 1.492(b), (c) and (d) (presentation of extra claims)

3. 37 CFR 1.17 (application processing fees)

4. 37 CFR 1.492(e) and (f) (surcharge fee for filing declaration and/or filing an English translation of an International Application later than 30 months after the priority date)

This application and items attached are being transmitted before the 30 month claimed priority date.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

August 29, 2001

By _____

Alan H. Bernstein
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Attorney Docket No. C1190/20009
PTO Customer No. 03000

Applicants : Laurent DI COSTANZO et al.

Title : ORALLY DISPERSIBLE TABLET WITH LOW FRIABILITY AND METHOD FOR PRODUCING SAME

The following documents are submitted for the above-identified invention for entry into the U.S. National stage under 35 U.S.C. §371, based on the International Application No. PCT/FR00/00495, which includes the following:

1. Two (2) pages of Transmittal Letter to the United States Elected Office (EO/US);

2. Two (2) pages Calculation sheet, in duplicate

3. Cover sheet of International Publication No. WO 00/51568

4. English translation of PCT/FR00/00495

5 A FIRST preliminary amendment, and attached Abstract.

6 Return Receipt Post Card

"Express Mail" Mailing Label No. EL 781 457 486 US
Date of Deposit August 29, 2001

I hereby certify that the above-identified documents are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR l.l0 on the date indicated above and is addressed to BOX PCT, Commissioner for Patents, Washington, D.C. 2023l, Attention RO/EO/US

Marie Trahey

Marie Trahey

AUTHORIZATION TO CHARGE ADDITIONAL FEES

The Commissioner is hereby authorized to charge the following additional fees which may be required by this paper and during the entire pendency of this application to counsel's deposit account no. 03-0075:

1. 37 CFR 1.492(a)(1), (2), (3) and (4) (filing fees)
2. 37 CFR 1.492(b), (c) and (d) (presentation of extra claims)
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This application and items attached are being transmitted before the 30 month claimed priority date.

Respectfully submitted,

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August 29, 2001

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PATENT
Attorney Docket No.: C1190/20009
PTO Customer No.: 03000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

Applicants	:	Laurent DI COSTANZO Edouard Andre GENDROT Mathieu Ernest Jean-Baptiste DI COSTANZO Charles, Andre CHAUVEAU
Serial No.	:	U.S. National Phase Application of PCT/FR00/00495 Filed on November 3, 1999
U.S. Filing Date	:	August 29, 2001
For	:	ORALLY DISPERSIBLE TABLET WITH LOW FRIABILITY AND METHOD FOR PRODUCING SAME

PRELIMINARY AMENDMENT

BOX PCT
Commissioner for Patents
Washington, D.C. 20231

Sir:

IN THE CLAIMS:

3. Tablet in accordance with Claim 1 wherein the lubricating agent is selected from among the pharmaceutically acceptable lubricating agents which have a melting point of at least 35°C, and preferably higher than 50°C.

4. Tablet in accordance with Claim 1 wherein the lubricating agent is selected from the group including magnesium stearate, sodium stearyl fumarate, stearic acid and micronized polyoxyethylene glycol.

5. Tablet in accordance with Claim 1 wherein the lubricating agent is magnesium stearate.

6. Tablet in accordance with Claim 1 wherein the quantity of lubricating agent is in the range 0.2 to 10 parts per 1000 (weight of lubricating agent / total weight of tablet), and is preferably in the range 3 to 6 parts per 1000 (weight of lubricating agent / total weight of tablet).

7. Tablet in accordance with Claim 1 wherein the lubricating agent has a particle size distribution such that its constituent particles adhere when it is sprayed against a surface, preferably less than 30 microns and more preferably still, less than 10 microns.

8. Tablet in accordance with Claim 1 wherein the disintegrating agent is selected from the group including in particular cross-linked sodium carboxymethylcellulose, known in the industry as croscarmellose, crospovidone and their mixtures.

9. Tablet in accordance with Claim 1 wherein the mixture of excipients may include a permeabilising agent, a solubilising agent, sweeteners, flavors and colorings.

10. Tablet in accordance with Claim 1 wherein said tablet is designed to be packaged in blisters composed entirely of aluminum, which may in addition include a cover of a plastic material which is to be torn off before opening.

11. Process for the production of a tablet in accordance with Claim 1 wherein the process involves the following sequence of steps:

choosing, firstly, an active substance in the form of coated microcrystals or microgranules, and secondly, a set of excipients including a disintegrating agent, a soluble agent, and also a lubricating agent;

mixing the active substance and the excipients with the exception of at least the greater part of the lubricating agent;

feeding a quantity of this mixture necessary to form a tablet into the cavity of a compression device within which

the mixture is to be compressed and onto the walls of which the necessary quantity of lubricating agent has been applied in advance;

compressing the mixture and ejecting the tablet formed.

REMARKS

Claims 3-11 have been amended to depend on Claim 1, and to eliminate multiple dependency in those claims. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

The Abstract is also attached hereto to comply with the requirements of 37 C.F.R. § 1.72(b).

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
BERNSTEIN & POKOTILOW, LTD.

By _____

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Version with markings to show changes made

3. Tablet in accordance with Claim 1 wherein ~~or Claim 2, characterized in that~~ the lubricating agent is selected from among the pharmaceutically acceptable lubricating agents which have a melting point of at least 35°C, and preferably higher than 50°C.

4. Tablet in accordance with Claim 1 wherein ~~one of Claims 1 to 3, characterized in that~~ the lubricating agent is selected from the group including magnesium stearate, sodium stearyl fumarate, stearic acid and micronized polyoxyethylene glycol.

5. Tablet in accordance with Claim 1 wherein ~~one of Claims 1 to 4, characterized in that~~ the lubricating agent is magnesium stearate.

6. Tablet in accordance with Claim 1 wherein ~~one of Claims 1 to 5, characterized in that~~ the quantity of lubricating agent is in the range 0.2 to 10 parts per 1000 (weight of lubricating agent / total weight of tablet), and is preferably in the range 3 to 6 parts per 1000 (weight of lubricating agent / total weight of tablet).

7. Tablet in accordance with Claim 1 wherein ~~one of Claims 1 to 6, characterized in that~~ the lubricating agent has a particle size distribution such that its constituent particles adhere when it is sprayed against a surface, preferably less than 30 microns and more preferably still, less than 10 microns.

8. Tablet in accordance with Claim 1 wherein ~~one of Claims 1 to 7, characterized in that~~ the disintegrating agent is selected from the group including in particular cross-linked sodium carboxymethylcellulose, known in the industry as croscarmellose, crospovidone and their mixtures.

9. Tablet in accordance with Claim 1 wherein ~~one of Claims 1 to 8, characterized in that~~ the mixture of excipients

may include a permeabilising agent, a solubilising agent, sweeteners, flavors and colorings.

10. Tablet in accordance with Claim 1 wherein said tablet ~~one of Claims 1 to 9, characterized in that it~~ is designed to be packaged in blisters composed entirely of aluminum, which may in addition include a cover of a plastic material which is to be torn off before opening.

11. Process for the production of a tablet in accordance with Claim 1 wherein ~~one of Claims 1 to 10, characterized in that~~ the process involves the following sequence of steps:

choosing, firstly, an active substance in the form of coated microcrystals or microgranules, and secondly, a set of excipients including a disintegrating agent, a soluble agent, and also a lubricating agent;

mixing the active substance and the excipients with the exception of at least the greater part of the lubricating agent;

feeding a quantity of this mixture necessary to form a tablet into the cavity of a compression device within which the mixture is to be compressed and onto the walls of which the necessary quantity of lubricating agent has been applied in advance;

compressing the mixture and ejecting the tablet formed.

Abstract:

ORALLY DISPERSIBLE TABLET

WITH LOW FRIABILITY AND METHOD FOR PRODUCING SAME

The invention concerns a rapidly disintegrating tablet similar to those designed to disintegrate in the mouth on contact with saliva in less than 30 seconds, forming an easy-to-swallow suspension, and based on an active substance in the form of coated microcrystals or microgranules and a mixture of excipients including at least a disintegrating agent, a soluble agent and a lubricating agent. The invention is characterized in that the lubricating agent is in powder form and is distributed at least for the greater part on the tablet surface and its friability, measured as specified in the French Pharmacopoeia (10th Edition, V.5.1 - Friability of Tablets, January 1993), is less than 1 %, and preferably less than 0.5 %, whereby said tablet can be packaged by standard processes, and has the required and adequate hardness to enable it to be removed with ease from the blister pack in which it is packaged, by perforating the seal thereof by pushing the tablet, with a substantially reduced risk of the tablet breaking during removal. The invention also concerns the method for producing said tablet.

I, Philip Gibson, verify that the document attached as Exhibit A is a true and correct English-language translation of the text of International Patent Application No. PCT/FR00/00495 attached as Exhibit B. I have been warned that wilful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001) and may jeopardize the validity of the application or any patent issuing thereon. All statements herein made of my own knowledge are true and all statements made on information and belief are believed by me to be true.

Signed: P Gibson

Name: Philip Gibson

Dated this 31st day of July 2001

ORALLY DISPERSIBLE TABLET WITH LOW FRIABILITY AND METHOD FOR PRODUCING SAME

The invention concerns an orally dispersible tablet, that is to say a rapidly disintegrating tablet similar to those designed to disintegrate in the mouth on contact with saliva, preferably in less than 40 seconds or even in less than 30 seconds. The invention also concerns the process for producing this tablet.

Previously known rapidly disintegrating tablets, for example those described by the Applicant Company in FR 97 09233, FR 98 14034, FR 92 08642 and FR 91 09245, often display high friability, and this requires special precautions when they are being transported and packaged, limiting the choice of packaging used.

The aim of this invention is primarily to provide tablets of the type concerned, having a pleasant taste and with a friability (measured as specified in the French Pharmacopoeia (10th Edition, V.5.1 - Friability of Tablets, January 1993), i.e. a hardness and resistance to abrasion, which enable them to be packaged and transported by conventional means, as well as to ensure ease of use by the patient.

The Applicant has found, surprisingly and unexpectedly, that it was possible to incorporate all these properties, some of which may appear incompatible with others, in a rapidly disintegrating tablet similar to those which are designed to disintegrate in the mouth in less than 30 seconds on contact with saliva, forming an easily-swallowed suspension. These tablets are based on an active substance in the form of coated microcrystals or microgranules and a mixture of excipients including at least one disintegrating agent, a soluble agent and a lubricating agent, and prior to compression at least the greater part of the lubricating agent is no longer present in

the mixture of excipients, but is brought into contact with the outer surface of the mass that will form the subsequent tablet.

A tablet of this sort may be packaged by standard operations, that is to say using conventional industrial machinery. The tablet is sufficiently hard to enable it to be removed easily from the blister in which it is packaged, by tearing, perforating or breaking the seal of the blister pack by pushing the tablet, with a substantially reduced risk of the tablet breaking.

The tablet according to this invention is therefore characterized in that a major amount of the lubricating agent which is used in its composition and which is in powder form, is distributed on the tablet surface, and by the fact that its friability, measured as specified in the French Pharmacopoeia (10th Edition, V.5.1 - Friability of Tablets, January 1993), is less than 1 %, and preferably less than 0.5 %.

The lubricating agent is chosen from pharmaceutically acceptable lubricating agents which have a melting point of at least 35°C and preferably higher than 50°C.

Preferably, the lubricating agent is selected from the group comprising in particular magnesium stearate, sodium stearyl fumarate, stearic acid, micronized polyoxyethylene glycol (micronized Macrogol 6000), leucine, sodium benzoate and their mixtures.

The quantity of lubricating agent employed in the tablet according to this invention is in the range 0.2 to 10 parts per thousand (weight of lubricating agent / total weight of tablet), and is preferably in the range 3 to 6 parts per thousand.

According to a preferred embodiment of the tablet according to the invention, the entire amount of lubricating agent is distributed on the outer surface of the tablet.

It must be stressed that this quantity is up to ten times less than that which has been required in known rapidly

disintegrating tablets of the type in question, in which the lubricating agent is distributed within the excipient.

The particle size distribution of the lubricating agent in powder form is such that its constituent particles adhere to a surface when it is sprayed thereon.

According to a preferred embodiment, this particle size is less than 30 microns and is preferably less than 10 microns.

The disintegrating agent is selected from the group including in particular cross-linked sodium carboxymethylcellulose, known in the industry as croscarmellose, crospovidone and their mixtures.

The soluble agent is preferably a diluent soluble agent with binding properties, such as, in particular, a polyol. This soluble agent can advantageously be selected in accordance with the description given in patent applications FR 97 09233 or FR 98 14034 in the name of the Applicant.

According to a preferred embodiment of the tablet according to the invention, the mixture of excipients includes a permeabilising agent, a solubilising agent, sweeteners, flavors and coloring agents.

The permeabilising agent used may be a compound selected from the group including in particular silicas with a high affinity for aqueous solvents, such as precipitated silica, better known by the brand name SYLOID®, colloidal silica better known by the name of AEROSIL® 200, maltodextrines, betacyclodextrines and their mixtures.

The sweetener may be chosen from the group including in particular aspartame, potassium acesulfam , sodium saccharinate, neohesperidine didrochalcone and their mixtures.

The flavorings and coloring agents are those normally used in pharmaceutical manufacture for the production of tablets.

Any active substance which can be employed in rapidly disintegrating tablets of the type in question may be used to advantage in the tablets concerned in this invention.

With regard to active substances, at least one of those may be used from the group including gastrointestinal sedatives, antacids, analgesics, anti-inflammatory drugs, coronary vasodilators, peripheral and cerebral vasodilators, anti-infective agents, antibiotics, antiviral agents, antiparasitic agents, anti-cancer drugs, anxiolytics, neuroleptics, central nervous system stimulants, antidepressants, anti-histamine substances, anti-diarrhoeal substances, laxatives, dietary supplements, immunodepressants, cholesterol-lowering agents, hormones, enzymes, antispasmodics, anti-anginal drugs, drugs acting on heart rhythm, drugs used in the treatment of arterial hypertension, anti-migraine substances, drugs affecting coagulation of the blood, anti-epileptic substances, muscle relaxants, drugs used in the treatment of diabetes, drugs used in the treatment of thyroid disorders, diuretics, appetite suppressants, anti-asthmatic drugs, expectorants, antitussives, mucus regulators, decongestants, hypnotics, anti-nausea substances, haematopoietic agents, substances inducing the elimination of uric acid, plant extracts, contrast media.

In the case of 17 mm diameter tablets according to the invention, the hardness is advantageously greater than 20 N, and preferably greater than 40 N, or more preferably still, greater than 80 N. This hardness is in all cases at least equal to the force needed to break the seal covering the blister in which the tablet is packed.

The friability of the tablets concerned in the invention, measured according to the procedure described in the French Pharmacopoeia, is less than 1 %, and preferably less than 0.5 %.

The largest dimension of the tablets concerned in the invention may be greater than 5 mm, or even 17 mm, and may reach 25 mm.

Conventional tablets of this size have a tendency to break when they are removed for administration, from the blisters in which they are packed, especially when the blister is composed entirely of a metallic material such as aluminum.

Due to their low friability, breakage of this sort does not occur in the case of tablets according to the invention, which are therefore particularly suitable for packaging in blisters composed entirely of aluminum.

Indeed, the high resistance of the tablets in the invention to breaking enables the risks of tablets breaking to be reduced substantially and enables the tablet to be removed with ease from the blister by tearing, perforating or breaking the seal of the blister by pushing the tablet according to the invention.

In addition, the tablet according to the invention enables child safety standards to be met, as it can be kept in doubly protected blisters, that is to say blisters than can be torn and/or peeled open, and the risk of breakage when removing a tablet from packaging other than a non-peelable blister pack is substantially reduced.

It is therefore possible to package tablets according to the invention in blisters made entirely of aluminum of a substantial thickness providing complete moisture-proofing and thus enabling a commercial product to be obtained which has excellent storage properties.

With regard to the production of tablets according to the invention, the process according to the invention is set out below.

Processes are already known for the production of tablets of conventional composition, which necessarily include the usual and significant quantities of lubricating agent - generally

representing 0.5 to 2 % of the weight of the tablet - in a mixture with their other constituents. The lubricating agent not only facilitates compression but also aids the flow of the powder mixture. These processes employ devices such as that described in patent EP 673 280, which are suitable for spraying lubricating agent onto the dies of compression machines to limit or prevent sticking of the compression machine.

The tablets obtained by these processes do not exhibit the beneficial properties which were set out above in relation to the tablets according to the invention.

The latter may be obtained by employing the process according to the invention, which consists of the following sequence of steps:

- choosing, firstly, an active substance in the form of coated microcrystals or microgranules, and secondly, a set of excipients including a disintegrating agent, a soluble agent, as well as a lubricating agent;

- mixing the active substance and the excipients with the exception of at least the major part of the lubricating agent;

- feeding a quantity of this mixture necessary to form a tablet into the cavity of a compression device within which the mixture is to be compressed and onto the walls of which the necessary quantity of lubricating agent has been applied in advance;

- compressing the mixture and ejecting the tablet formed.

The process according to the invention has the advantage which arises from the fact that the compression forces that need to be applied to obtain the tablet are appreciably lower than those used in known processes, yet resulting in a hardness that is equal to or even greater than that of conventional tablets.

According to a preferred embodiment of the process according to the invention, the compression forces are in the range 3 kN to 50 kN, preferably in the range 4 kN to 40 kN, and more preferably still, in the range 5 kN to 25 kN.

Even with these compression forces, it is possible to obtain large-sized tablets with a hardness greater than 20 N, and preferably greater than 40 N, and more preferably still, greater than 80 N.

It must be stated in addition that with prior art tablets, it is necessary to modify the quantity of lubricating agent incorporated in the mixture of excipients depending on the active substance used in the tablet. In contrast, and in an entirely advantageous way, the process according to the invention does not require this sort of modification of the formulation of the excipient mixture depending on the active substance used.

The invention can be better understood with the aid of non-limiting examples which are given below and which relate to advantageous embodiments of the invention.

EXAMPLE 1:

Paracetamol 500 mg tablet.

Table 1 shows the content per tablet and the percentage composition of this tablet.

TABLE 1

CONSTITUENTS	CONTENT PER TABLET	PERCENTAGE COMPOSITION
Coated paracetamol	548.70	39.17
Mannitol for direct compression	514.80	36.74
Mannitol crystalline powder	171.50	12.24
Crospovidone	120.00	8.57
Aspartame	40.00	2.86
Blackcurrant flavor	5.00	0.36
Magnesium stearate	0.90	0.06
TOTAL	**1400.70 mg**	**100.0 %**

This tablet is produced as described below.

The microcrystals of paracetamol are fed into a fluid-bed plant and a dispersion of EUDRAGIT E 100, EUDRAGIT NE 30 D and colloidal silica in ethanol is sprayed onto the microcrystals to obtain microcrystals coated with 10 % of polymer with the formulation given in Table 2 below.

All the excipients are sieved with the exception of the magnesium stearate, and the mixture consisting of the coated paracetamol and the excipients is homogenized in a dry mixer.

The next step is compression on a compression machine fitted with 17 mm diameter dies and punches; the walls of the dies and the punches are first sprayed with magnesium stearate to act as a lubricating agent (the excess quantity of magnesium stearate that does not adhere to the dies and punches is removed by suction before compression).

The compression force is in the range 16 kN to 25 kN, which produces tablets with a hardness of 80 Newtons.

The disintegration time in the mouth, of tablets produced in this way, is less than 30 seconds.

This time corresponds to the length of time between placing the tablet in the mouth when it comes into contact with the saliva, and the moment at which the suspension resulting from the disintegration of the tablet on contact with saliva is swallowed.

Its friability, measured according to the procedure described in the French Pharmacopoeia (10th Edition, V.5.1 - Friability of Tablets, January 1993), using a bladed friability tester, is less than 1 %.

The quantity of magnesium stearate distributed at the surface of the tablet is 0.9 mg or 0.64 parts per thousand.

Table 2

CONSTITUENTS	CONTENT PER TABLET	PERCENTAGE COMPOSITION
Coated paracetamol	500.00	91.12
Eudragit NE 30 D, dry	12.10	2.21
Eudragit E 100	24.30	4.43
Colloidal silica	12.30	2.24
TOTAL	**548.70 mg**	**100.0 %**

EXAMPLE 2:

Ibuprofen 200 mg tablet

Table 3 shows the unit content of this tablet.

TABLE 3

CONSTITUENTS	CONTENT PER TABLET	PERCENTAGE COMPOSITION
Coated ibuprofen granulate	256.20	36.60
Mannitol granulate	192.80	27.54
Mannitol powder	193.40	27.63
Croscarmellose	21.00	3.00
Precipitated silica	7.00	1.00
Aspartame	25.00	3.57
Lemon flavor	4.00	0.57
Magnesium stearate	0.60	0.09
TOTAL	**700.00 mg**	**100.00 %**

The excipients shown in Table 2 are screened through a sieve with a pore size of 1000 microns.

The various constituents are weighed out into separate containers of appropriate capacity.

The coated ibuprofen granules (whose formulation is given in Table 3 below), mannitol granulate, mannitol powder, croscarmellose, aspartame, precipitated silica and the flavoring are placed one after another in a mixer.

A homogeneous mixture is prepared.

The walls of the dies and the punches of a rotary compression machine are sprayed with magnesium stearate (the excess quantity of magnesium stearate is removed by suction).

The prepared mixture is fed into the dies of the rotary compression machine between the punches covered with magnesium stearate and it is compressed with a compression force of the order of 7 kN, in order to obtain tablets with the following characteristics:

- mean tablet weight in the range 665 mg to 735 mg;
- breaking strength in the range 20 N to 50 N;
- friability less than 1 %;
- mean disintegration time in the mouth less than 30 seconds.

This disintegration time corresponds to the length of time between placing the tablet in the mouth when it comes into contact with the saliva, and the moment at which the suspension resulting from the disintegration of the tablet on contact with saliva is swallowed.

The quantity of magnesium stearate in the final tablet is 0.6 mg or 0.8 parts per 1000.

TABLE 4

Formula of ibuprofen-coated granulate

CONSTITUENTS	CONTENT PER TABLET	PERCENTAGE COMPOSITION
Ibuprofen	200.00	78.06
Ethylcellulose	35.00	13.66
Precipitated silica	14.20	5.55
HPMC *	7.00	2.73
TOTAL	**256.20 mg**	**100.00 %**

* HPMC : hydroxypropylmethylcellulose

EXAMPLE 3:

Aspirin 500 mg tablet

Table 5 shows the unit content of this tablet.

TABLE 5

CONSTITUENTS	CONTENT PER TABLET	PERCENTAGE COMPOSITION
Coated aspirin granulate	564.00	40.29
Mannitol granulate	336.00	24.00
Mannitol powder	336.00	24.00
Crospovidone	120.00	8.57
Precipitated silica	14.00	1.00
Aspartame	14.40	1.03
Potassium acesulfam	9.60	0.89
Lemon flavor	5.00	0.36
Sodium stearate	0.90	0.06
TOTAL	**1400.00 mg**	**100.00 %**

The tablets are produced in the same way as in Example 1, using coated granulate with the formulation given in Table 6 below, and by compressing the tablets on a compression machine on which the walls of the dies and the punches have previously been coated by spraying with sodium stearyl fumarate.

TABLE 6

Formula of aspirin-coated granulate

CONSTITUENTS	CONTENT PER TABLET	PERCENTAGE COMPOSITION
Aspirin	500.00	88.85
Ethylcellulose	50.00	8.87
HPMC *	10.00	1.77
Colloidal silica	4.00	0.71
TOTAL	**564.00 mg**	**100.00 %**

* HPMC : hydroxypropylmethylcellulose

The tablets obtained in this manner exhibit the following characteristics:

- quantity of sodium stearyl fumarate: 0.9 mg or 0.64 parts per 1000
- breaking strength: 30 N to 60 N;
- friability: less than 1 %;
- disintegration time less than 30 seconds.

CLAIMS

1. A rapidly disintegrating tablet of the type designed to disintegrate in the mouth on contact with saliva in less than 30 seconds, forming an easy-to-swallow suspension, which contains an active substance in the form of coated microcrystals or microgranules, and a mixture of excipients including at least one disintegrating agent, a soluble agent and a lubricating agent, wherein the lubricating agent is in powder form and at least a major amount of it is distributed on the tablet surface, and that its friability, measured as specified in the French Pharmacopoeia (10th Edition, V.5.1 - Friability of Tablets, January 1993), is less than 1 %, and preferably less than 0.5 %, whereby said tablet can be packaged by standard processes and has the required and adequate hardness to enable it to be removed with ease from the blister pack in which it is packed, by perforating the seal thereof by pushing the tablet, with a substantially reduced risk of the tablet breaking during removal.

2. Tablet in accordance with Claim 1, wherein its largest dimension is greater than 5 mm, preferably greater than 17 mm, and capable of reaching 25 mm.

3. Tablet in accordance with Claim 1 or Claim 2, wherein the lubricating agent is selected from among the pharmaceutically acceptable lubricating agents which have a melting point of at least 35°C, and preferably higher than 50°C.

4. Tablet in accordance with one of Claims 1 to 3, wherein the lubricating agent is selected from the group including magnesium stearate, sodium stearyl fumarate, stearic acid and micronized polyoxyethylene glycol.

5. Tablet in accordance with one of Claims 1 to 4, wherein the lubricating agent is magnesium stearate.

6. Tablet in accordance with one of Claims 1 to 5, wherein the quantity of lubricating agent is in the range 0.2 to 10 parts per 1000 (weight of lubricating agent / total weight of tablet), and is preferably in the range 3 to 6 parts per 1000 (weight of lubricating agent / total weight of tablet).

7. Tablet in accordance with one of Claims 1 to 6, wherein the lubricating agent has a particle size distribution such that its constituent particles adhere to a surface when sprayed thereupon, preferably less than 30 microns and more preferably still, less than 10 microns.

8. Tablet in accordance with one of Claims 1 to 7, wherein the disintegrating agent is selected from the group including in particular cross-linked sodium carboxymethylcellulose, known in the industry as croscarmellose, crospovidone and their mixtures.

9. Tablet in accordance with one of Claims 1 to 8, wherein the mixture of excipients may include a permeabilising agent, a solubilising agent, sweeteners, flavors and coloring agents.

10. Tablet in accordance with one of Claims 1 to 9, which is designed to be packaged in blisters composed entirely of aluminum, which may in addition include a cover of a plastic material which is to be torn off before opening.

11. Process for the production of a tablet in accordance with one of Claims 1 to 10, wherein the process involves the following sequence of steps:

- choosing, firstly, an active substance in the form of coated microcrystals or microgranules, and secondly, a set of excipients including a disintegrating agent, a soluble agent, as well as a lubricating agent;

- mixing the active substance and the excipients with the exception of at least a major amount of the lubricating agent;

- feeding a quantity of this mixture necessary to form a tablet into the cavity of a compression device within which the mixture is to be compressed and onto the walls of which the necessary quantity of lubricating agent has been applied in advance;

- compressing the mixture and ejecting the tablet formed.

12. Process in accordance with Claim 11, wherein the compression forces are in the range 3 kN to 50 kN, preferably in the range 4 kN to 40 kN, or more preferably still, in the range 5 kN to 25 kN.

Abstract:

ORALLY DISPERSIBLE TABLET

WITH LOW FRIABILITY AND METHOD FOR PRODUCING SAME

The invention concerns a rapidly disintegrating tablet similar to those designed to disintegrate in the mouth on contact with saliva in less than 30 seconds, forming an easy-to-swallow suspension, and based on an active substance in the form of coated microcrystals or microgranules and a mixture of excipients including at least a disintegrating agent, a soluble agent and a lubricating agent. The invention is characterized in that the lubricating agent is in powder form and is distributed at least for the greater part on the tablet surface and its friability, measured as specified in the French Pharmacopoeia (10th Edition, V.5.1 - Friability of Tablets, January 1993), is less than 1 %, and preferably less than 0.5 %, whereby said tablet can be packaged by standard processes, and has the required and adequate hardness to enable it to be removed with ease from the blister pack in which it is packaged, by perforating the seal thereof by pushing the tablet, with a substantially reduced risk of the tablet breaking during removal. The invention also concerns the method for producing said tablet.

 #3

PATENT
Attorney Docket No. C1190/20009
Customer No. 03000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
REFUND SECTION, ACCOUNTING DIVISION, OFFICE OF FINANCE

Applicants	:	Laurent DI COSTANZO, Edouard Andre' GENDROT, Mathieu Ernest Jean-Baptist DI COSTANZO and Charles Andre' CHAUVEAU
Serial No.	:	09/914,544
Filed	:	U.S. National Phase Application of PCT/FR00/00495 Filed February 29, 2000
For	:	ORALLY DISPERSIBLE TABLET WITH LOW FRIABILITY AND METHOD FOR PRODUCING SAME

SUBMISSION OF DECLARATION FOR PATENT APPLICATION

Box PCT
Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants enclose a facsimile of the Declaration for Patent Application, which should be placed in the file of this application. An original copy of this Declaration will be provided upon request from the U.S. Patent Office.

The Applicants are not entitled to small entity status. Accordingly, the United States Patent and Trademark Office is authorized to charge our deposit Account No. 03-0075 the sum of One Hundred Thirty Dollars ($130.00) or any other fee as the surcharge appropriate herein. A duplicate copy of this document is enclosed herewith.

Also enclosed, in duplicate, is a Petition for Extension of Time to permit the timely filing of the Declaration, along with authorization to charge our account for the Petition fee.

We further enclose the Notification of Missing Parts.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

March 8, 2002

By_____

Robert S. Silver
Registration No. 35,681
12th Floor, Seven Penn Center
1635 Market Street
Philadelphia, PA 19103-2212
(215) 567-2010

CERTIFICATE OF MAILING

I hereby certify that the foregoing SUBMISSION OF DECLARATION FOR PATENT APPLICATION, in duplicate, and attached Declaration for Patent Application, Petition for Extension of Time, in duplicate and Notification of Missing Parts, re application Serial No. 09/914,544, are being deposited with the United States Postal Service as First Class Mail, postage prepaid, in an envelope addressed to: Box PCT, Commissioner for Patents, Washington, D.C. 20231, this 8th day of March, 2002.

_____

Robert S. Silver

#3

PATENT
Attorney Docket No. C1190/20009
Customer No. 03000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
REFUND SECTION, ACCOUNTING DIVISION, OFFICE OF FINANCE

Applicants	:	Laurent DI COSTANZO, Edouard Andre' GENDROT, Mathieu Ernest Jean-Baptist DI COSTANZO and Charles Andre' CHAUVEAU
Serial No.	:	09/914,544
Filed	:	U.S. National Phase Application of PCT/FR00/00495 Filed February 29, 2000
For	:	ORALLY DISPERSIBLE TABLET WITH LOW FRIABILITY AND METHOD FOR PRODUCING SAME

PETITION FOR EXTENSION OF TIME

BOX PCT
Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant hereby petitions for a three (3) month extension of time, up to and including March 10, 2002, for the purpose of permitting the timely filing of the enclosed Submission of Declaration For Patent Application and attached Declaration For Patent Application.

Please charge the three-month extension fee of Nine Hundred Twenty Dollars ($920.00) for a large entity, and/or any additional fees associated with this Petition For Extension of Time, to Deposit Account No. 03-0075.

04/08/2002 AYILMAZ 00000004 030075 09914544
01 FC:128 1960.00 CH

A duplicate copy of this Petition is enclosed.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

March 8, 2002

By _____
Robert S. Silver
Reg. No. 35,681
12th Floor, Seven Penn Center
1635 Market Street
Philadelphia, PA 19103-2212
(215) 567-2010

USA
Flashtab IV

DECLARATION FOR PATENT APPLICATION

Docket Number (optional)_____

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ORALLY DISPERSIBLE TABLET WITH LOW FRIABILITY AND METHOD FOR PRODUCING SAME

the specification of which is attached hereto unless the following box is checked:

Was filed on 29 February 2000 as United States Application Number or PCT International Application Number PCT/FR00/00495 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR1.56. I hereby claim foreign priority benefits under 35 U.S.C. ' 119 (a)(d) or ' 365(b) of any foreign application(s) for patent or inventor's certificate, or ' 365 (a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventors certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Claimed
99 02516	FRANCE	1er th. march 1999	X Yes
(Number)	(Country)	(Day/Month/Year Filed)	No
_____	_____	_____	___ Yes ___ No
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. '119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. ' 120 of any United States application(s) or ' 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C.' 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR ' 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

FR00/00495	29th February 2000	PENDING
(Application Number)	(Filing Date)	(Status-patented, pending, abandoned)
_____	_____	_____
(Application Number)	(Filing Date)	(Status-patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Alan H. Bernstein (Registration No. 19,315); Stanley H. Cohen (Registration No. 20,235); Manny D. Pokotilow (Registration No. 22,492); Barry A. Stein (Registration No. 25,257); Martin L. Faigus (Registration No. 24,364); Eric S. Marzluf (Registration No. 27,454); Robert S. Silver (Registration No. 35,681); Scott M. Slomowitz (Registration No. 39,032); Michael J. Berkowitz (Registration No. 39,607); David M. Tener (Registration No. 37,054); James J. Kozuch (Registration No. 39,733); Frank M. Linguiti (Registration No. 32,424); Gary A. Greene (Registration No. 38,897); Marilou E. Watson (Registration No. 42,213); Michael J. Cornelison (Registration No. 40,396); and Christopher Marrone (Registration No. 46,101), care of Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd., 12th Floor, Seven Penn Center, 1635 Market Street, Philadelphia, Pennsylvania 19103-2212, my attorneys with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor (given name, family name) Laurent DI COSTANZO

Inventor's signature Laurent Di Costanzo Date 1-00

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Second Inventor's signature Edouard GENDROT Date

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Third Inventor's signature Mathieu Di Costanzo Date

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4-00

Full name of fourth inventor, if any (given name, family name) Charles, André CHAUVEAU

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